## REMARKS

Claims 1-14 and 25-34 are pending in the application. Claims 9 and 12-14 have now been cancelled.

Support for the addition of the term "an imaging agent suitable for use in Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) or Magnetic Resonance Imaging (MRI)" to claim 1 may be found, for example, on page 7, pages 24-25 and pages 30-31 of the specification. At the time of filing of the specification, there were ample teachings in the art as to which imaging agents were those suitable for use in Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) or Magnetic Resonance Imaging (MRI). Thus, one of skill in the art would have recognized which of the various agents in the lists of agents disclosed in the specification were those imaging agents suitable for use in Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) or Magnetic Resonance Imaging (MRI). See, for example, the inventor's own work, published in 1986 (Exhibit A), which lists suitable agents for PET and SPECT, a 1975 article on certain biomedically important positron-emitting radionuclides (Exhibit B), as well as various abstracts to review articles on magnetic resonance contrast agents (Exhibit C), which Applicants can provide in full if necessary.

Support for the addition of the term "said imaging agent is selected from the group consisting of: an unpaired spin atom, a free radical, a paramagnetic contrast agent and a metal chelate" to claim 2 may be found, for example, on page 7, pages 24-25 and pages 30-31 of the specification.

Support for the addition of the term "said imaging agent is a paramagnetic contrast agent selected from the group consisting of: gadolinium, cobalt, nickel, manganese, and iron" to claim 3 may be found, for example, on page 25 of the specification.

Support for the addition of the term "said imaging agent is a radiolabel selected from the group consisting of: $^{131}I$, $^{123}I$ , $^{99m}Tc$, $^{18}F$, $^{68}Ga$, $^{67}Ga$, $^{72}As$, $^{89}Zr$, $^{64}Cu$, $^{62}Cu$, $^{111}In$, $^{203}Pb$, $^{198}Hg$, $^{11}C$, $^{97}Ru$, and $^{201}Tl$" to claim 5 and for the addition of the term "wherein the radiolabel is a chelate" to claim 6 may be found, for example, on page 25 of the specification.

Support for the addition of the term "said imaging agent is an iron, lanthanide or gadolinium unpaired spin atom or free radical" to claim 7 may be found, for example, on page 7 of the specification.

Support for the other amendments may be found throughout the specification and in the claims as originally filed.

Amendment of the pending claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. No new matter has been added by the present amendments. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the option to prosecute the pending claims further, or other ones, in the instant or a subsequent patent application.

Applicants thank Examiner for removing some of the rejections in the last Office Action, for withdrawing the finality of the previous Office Action and for entering Applicants' submission.

## CLAIM REJECTIONS

### *Claim Objections*

The Examiner has objected to claims 2 and 9 as being of improper dependent form because they allegedly do not serve to further limit their parent claims 1 and 8, which claims 1 and 8 allegedly "explicitly recite that the targeting moiety may be a lipid." Applicants have amended claims 1-2 and 8-9 such that this rejection is rendered moot.

The Examiner has also objected to claim 3 as being of improper dependent form because it allegedly does not serve to further limit parent claim 1 by reciting detectable labels that are photoreactive. Applicants have amended claim 3 such that this rejection is rendered moot.

Accordingly, Applicants respectfully request that the Examiner withdraw the present objections.

### *Rejection of claims under 35 U.S.C. § 112, second paragraph*

*Claim 1*

The Examiner has rejected claim 1 as indefinite for reciting "non-photoreactive" when its dependent claims allegedly recite photoreactive fluorescent labels. The Examiner has further rejected claim 1 as indefinite because it contains the term "receptor-binding internalized ligand." Applicants have amended claim 1 such that these terms are no longer recited. Thus, the amendment obviates the rejection.

Accordingly, Applicants respectfully request that the Examiner withdraw the present rejections of claim 1.

*Claim 8*

The Examiner has rejected claim 8 as having insufficient antecedent basis for the limitation "said construct." Applicants have amended claim 8 from reciting "conjugate" to recite "construct," among other things, thus obviating this rejection. Applicants respectfully request the withdrawal of the present rejection.

*Claims 9-14*

The Examiner has rejected claims 9-14, which recite "a ... construct as in claim 8" as having no antecedent basis for this limitation, and claims 30-34 because they are dependent on claim 11. As discussed above, Applicants have amended claim 8 from reciting "conjugate" to reciting "construct," thus obviating these rejections. Applicants respectfully request the withdrawal of these rejections.

*Claims 12-14*

The Examiner has rejected claims 12-14, which recite "said label" as having no antecedent basis for this limitation. Applicants have canceled claims 12-14, thus obviating this rejection. Applicants respectfully request the withdrawal of the present rejection.

***Rejection of claims under 35 U.S.C. § 112, first paragraph***

The Examiner has rejected claims 1 and 8 and their dependent claims for lack of enablement due to the limitation "wherein said construct does not comprise a receptor-binding internalized ligand." Applicants have amended claims 1 and 8 such that this term is no longer recited, thus obviating the rejection. Applicants respectfully request that the Examiner remove the present rejection for lack of enablement.

***Rejection of claims under 35 U.S.C. § 102(e) over Papahadjopoulos, et al.***

The Examiner has maintained the anticipation rejection of claims 1-3, 5, and 8-10 over Papahadjopoulos et al. (U.S. Patent No. 6,410,049). Applicants have amended claim 1 such that it no longer recites the term "lipid." Claims 2-3, 5 and 8-10 are dependent from claim 1. Therefore, the instantly claimed invention is not anticipated by the Papahadjopoulos reference, which teaches the use of various lipids complexed with nucleic acids and certain labels. Applicants respectfully request reconsideration and withdrawal of the present rejection.

***Rejection of claims under 35 U.S.C. § 102(e) over Rothschild, et al.***

The Examiner has maintained the anticipation rejection of claims 1-3, 5-10, and 12-14 over Rothschild et al. (U.S. Patent No. 6,589,736). The Examiner alleged that Rothschild et al.

teaches "conjugates comprising an oligonucleotide that targets to a sequence of interest (antisense sequences), a protein targeting moiety, a polypeptide therapeutic agent and a fluorescent or chemiluminescent detectable label, which targeting moiety localizes to a site in an organism, and wherein the targeting moiety, detectable label and nucleotide are optionally coupled covalently to each other".

Claim 1 has been amended such that it no longer recites fluorescent or chemiluminescent detectable labels for reasons unrelated to the instant rejection over Rothschild. Claims 2-3 and 5-10 are dependent on 1, and claims 12-14 have been cancelled. Therefore, the invention as claimed is not anticipated by the Rothschild reference and the instant rejection has been rendered moot. Applicants respectfully request reconsideration and withdrawal of the present rejection.

## CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and notification of such is respectfully requested.

If, for any reason, a telephonic conference with the Applicants would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Agent at the telephone number provided below.

Respectfully submitted,

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June 9, 2005

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EXHIBIT A



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## FEATURES

# Musings on PET and SPECT

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AT A RECENT international meeting two speakers discussed the relative virtues of positron-emission tomography (PET) and single photon–emission computed tomography (SPECT) for use in cardiology. Several points were raised in favor of each technique, suggesting that one of the methods might be preferable for evaluation of the cardiac patient. It is unclear whether this competitive position is necessarily correct, since there are virtues to each of the techniques, and both are capable of providing timely information of value in patient care.

To appreciate the potential contribution of each technique to the evaluation of the patient with cardiovascular disease, it is helpful to review some of the salient features of each. The principles of instrumentation and range of radiopharmaceuticals for use with PET and SPECT are different. Positron systems position events by coincidence detection — two events occurring in a pair of detectors placed 180 degrees apart — within a specified short time interval. Single-photon systems limit the direction of photons entering the detector by collimation and then position the event in the detector electronically. As a result, single-photon systems are two to three orders of magnitude less sensitive than positron systems (i.e., for each unit of activity in the field of view of the detector, PET systems will have a higher count rate than SPECT). The sensitivity of SPECT systems has not been optimized nearly as well as that of PET ring systems. Most manufacturers of SPECT systems offer single- or two-detector instruments, leaving large gaps around the patient and no detector for photon interaction. Recently a three-detector system, arranged as three planes around the subject, was described by Technicare. This device, with fan-beam collimation, would improve sensitivity by almost an order of magnitude. Other multidetector approaches, such as the "Harvard" multidetector scanner, have been suggested to overcome the sensitivity problem. Even with additional detectors, however, the sensitivity of PET systems will remain substantially better than that of conventionally collimated SPECT systems.

Over the past 4 years, the technology of imaging devices has improved to a point where present-generation positron tomographs can provide a spatial resolution of 4 to 5 mm full width at half maximum (FWHM), while single-photon multidetector tomographs can record 8 to 10 mm FWHM. This difference in spatial resolution is likely to remain in favor of positron devices for the foreseeable future, since SPECT systems will be limited by the need for collimation.

The requirement for annihilation radiation produced via beta-plus decay defines both a major limitation and a major benefit of positron systems: Only photons of 511 keV can be imaged; however, the coincident detection system provides a straightforward means of correcting for photon attenuation. In contrast, single-photon systems can image nuclides with many different energies, ranging from 30 to greater than 511 keV, but there is no simple approach to correct for attenuation. Since positron-emitting radionuclides release beta radiation in the course of their decay, they deliver a larger amount of energy to the tissue than a comparable gamma-emitting nuclide. To minimize the radiation burden to the subject, positron-emitting radionuclides with short half-lives ($t\frac{1}{2}$s) are usually used. The difference in radiation burden with positron-emitting as compared with single photon–emitting nuclides is readily apparent when considering the radiation burden to bone from the two bone-seeking radiopharmaceuticals $^{18}F$ (physical $t\frac{1}{2} = 1.8$ hr) and $^{99m}Tc$-labeled pyrophosphate (physical $t\frac{1}{2} = 6$ hr) — 0.14 and 0.046 mrad/$\mu$Ci, respectively. The radiation burden from $^{18}F$ is threefold greater than that from technetium, despite the longer $t\frac{1}{2}$ of $^{99m}Tc$.

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Nature has deemed that the important radionuclides of carbon, oxygen, and nitrogen are positron emitters — with short physical t½s. As a result, these important radionuclides can be incorporated as intrinsic labels into common amino acids, drugs, and metabolic substrates, without altering the molecule under investigation. With positron-detection techniques and $^{11}$C-labeled radionuclides, for example, the short-term kinetics of many agents can be evaluated. The combination of the radiation burden and the 20 min physical t½ effectively precludes measurements that require more than about 2 hr of observation. However, even with this limitation, much can be defined about receptor interactions and metabolic precursor utilization. If information must be recorded for longer intervals, $^{18}$F may be employed as the radiolabel (as in fluorodeoxyglucose, vs $^{11}$C-deoxyglucose). However, if the process must be observed for more than about 6 hr (three t½s of $^{18}$F), positron-emitting nuclides are impractical.

Single-photon radiopharmaceuticals labeled with nuclides with decay schemes that do not include primary emission of beta particles or a high incidence of conversion electrons can be administered in multimillicurie quantities with an acceptable radiation burden. The physical t½ of the commonly used single-photon radiopharmaceuticals (hours to days) typically allows processes to be followed for intervals greater than 24 hr. At the other end of the t½ spectrum, the generator-produced ultra short–lived single-photon radionuclide $^{191m}$Ir (t½ 4.7 sec) can be repetitively administered in amounts of 50 to 100 mCi for bolus studies, or infused over intervals of 10 min to provide photon fluxes sufficient to record high count-density SPECT images.

Since the average adult heart occupies a volume of 400 ml, data should be recorded over an extended area to ensure complete sampling. While single-detector SPECT is relatively insensitive compared with PET, large-field scintillation cameras record data from an extended area, sampling both the zones of immediate interest and the surrounding tissue in the course of a single rotation. The contiguous data samples can be readily reconstructed into sagittal, coronal, and oblique images for interpretation. Although PET typically records three to five slices per acquisition, it is usually necessary to move the patient and record several sets of images to provide a data set suitable for sagittal, coronal, or oblique reconstructions.

Even with the ability of PET to produce quantitative data, in clinical studies of regional glucose utilization and fatty distribution results have been reported as relative intensities on images. This observation suggests that absolute measurements may not be required for some clinical decision making and that relative determinations of regional distribution of the specific function may suffice.

Some measurements can be made with either PET or SPECT, including determinations of the relative distribution of myocardial perfusion, detection of myocardial necrosis, measurement of regional and global ventricular function, and evaluation of the relative distribution of fatty acid uptake (table 1). To date no comparison of the relative sensitivity of the two techniques for the detection of myocardial ischemia in man is available. Indirect evidence suggests that the results may slightly favor PET when such a comparison is made. The question, however, is how much benefit will accrue from the use of PET and monovalent cations such as $^{82}$Rb compared with that resulting from the use of SPECT and one of the new isonitrile analogs.

The circumstances surrounding the measurement of metabolism, however, are different. Two major criticisms are usually leveled at SPECT imaging when this technique is suggested for the determination of metabolism: (1) the difficulty defining absolute radionuclide concentrations in the image due to the problems with attenuation correction, and (2) the need to evaluate the metabolism of the analog, in other words to define the impact of the structural alteration on the molecule caused by the addition of the "foreign" radiolabel. Since PET studies are usually performed with intrinsic labels (e.g., $^{11}$C-palmitate), the extensive data accumulated through the detailed studies performed with $^{14}$C-labeled and unlabeled palmitate can be directly applied to the imaging studies. Ultimately, the choice of technique will be based on the clinical importance of absolute measurements. If relative measurements are acceptable and the analogs reflect the behavior of the native compound to a substantial extent, SPECT may supply clinically valuable data.

The current practice of cardiovascular nuclear medicine suggests that the major applications of radionuclide imaging procedures fall into the three following categories: (1) detection of ischemia, (2) determination of regional and global function, and (3) determination of the site and extent of regional myocardial necrosis. Both PET and SPECT can be used to make these measurements. The SPECT methodology is widely available, and provides the majority of clinical data required for patient care. Research studies now suggest that the addition of measurements of glucose distribution in the myocardium may allow identification of ischemic but recoverable tissue. By virtue of radiopharmaceutical availability, this important mea-

**TABLE 1**
**Some measurements available with PET and SPECT**

| | Radionuclide | Method | Comments |
|---|---|---|---|
| Myocardial perfusion | $^{201}$Tl[1, 2] | SPECT | Ischemia/scar; improved contrast resolution compared with planar imaging |
| | $^{99m}$Tc ISN[A, 3, 4] | SPECT | Ischemia/scar; improved count rate permits gated tomographic imaging |
| | $^{82}$Rb[5] | PET | Ischemia/scar; improved contrast; short t½ permits repeat determinations in short intervals |
| | $^{15}$O-$H_2O$[6] | PET | Ischemia/scar; low contrast compared with Rb; permits repeat measurements in short interval |
| Metabolism | | | |
| Fatty acid | $^{11}$C-palmitate[7] | PET | Fatty acid catabolism via clearance measurements and metabolic model; defines ischemia as zones of relative retention |
| | $^{11}$C-modified fatty acid (BMHDA[B])[8] | PET | Fatty acid catabolism via uptake and/or steady-state measurement |
| | $^{123}$I-fatty acid[9-11] | Planar imaging | Complex clearance of radiolabel make absolute metabolic measurements impossible; useful for evaluation of relative regional catabolism |
| | $^{123}$I-phenyl[C] pentadecanoic acid[12] | SPECT | Fatty acid analog; has longer residence time than palmitate; defines ischemia as zone of increased retention |
| | $^{123}$I-modified fatty acids[D, 13] | SPECT | Minimal clearance; relative fatty acid uptake can be calculated; preliminary studies suggest comparison to perfusion can provide an indication of viability |
| Glucose utilization | $^{11}$C-deoxyglucose and F$^{18}$DG[14] | PET | Regional glucose utilization; zones of ischemia have increased uptake |
| Myocardial necrosis | $^{99m}$Tc-pyrophosphate[15, 16] | SPECT | Extent of acute necrosis |
| | $^{111}$In-antimyosin[17] | SPECT | Extent of acute necrosis |
| | $^{18}$F[18] | PET | Extent of acute necrosis |
| Global and regional function | $^{99m}$Tc-red cells[19-21] | SPECT | Ejection fraction; chamber volumes; regional wall motion |
| | $^{11}$C-CO (carboxyhemoglobin) | PET | Ejection fraction; chamber volumes; regional wall motion |

[A]ISN = isonitrile — one of a series of agents under development for the evaluation of myocardial perfusion (see references 3 and 4).

[B]BMHDA = $\beta$-methyl heptadecanoic acid — a long-chain fatty acid (17 carbon) modified by addition of a methyl group precludes $\beta$-oxidation, resulting in a long intracellular residence time of the radiolabel.

[C]To enhance the stability of the iodine label on the fatty acid molecule, both the ω-phenyl and terminal iodovinyl compounds have been synthesized. Both appear to have slightly-prolonged myocardial retention compared to 16-$^{123}$I-palmitate.

[D]$^{123}$I-modified fatty acids are a family of methyl substituted fatty acids including 15-[P-$^{123}$I-phenyl]-3-methylpentadecanoic acid, the 3,3 dimethyl substituted analog, and the 9-methyl substituted analog. The addition of the methyl group(s) prolong the intracellular residence time as above.

surement can only be made with PET. To the extent that this measurement will provide crucial data for patient care, the number of applications for PET will grow.

An alternative to the labeled glucose approach has been suggested to detect transient ischemia. Recent studies with both $^{11}$C-palmitate and $^{123}$I-phenylpentadecanoic acid indicate that zones of myocardial ischemia have a prolonged retention of radiolabeled fatty acids compared with retention in the adjacent normally perfused areas. When imaging is carried out for 20 to 30 min, retention of the radiolabel in these areas provides a "hot spot" signal in the zone of ischemia, since the radiolabel has cleared to a much greater extent in the normally perfused/normally metabolizing zones. As a result, fatty acid imaging with either PET or SPECT may be added to those methods utilizing PET and glucose analogs for the identification of areas of ischemia.

Despite the marked differences in technology, both PET and SPECT offer important windows to view myocardial physiology. As new pharmaceuticals and catheter techniques become available for the aggressive treatment of coronary thrombosis, the need to characterize the status of the myocardium is likely to increase. These considerations suggest that the future preponderance of each technique will be determined by its ability to provide timely information required for important clinical decisions.

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**EXHIBIT B**

# POSITRON RANGES OBTAINED FROM BIOMEDICALLY IMPORTANT POSITRON-EMITTING RADIONUCLIDES

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***Positron ranges were obtained experimentally for several nuclides used in scintigraphic imaging. The nuclides examined were $^{11}C$, $^{13}N$, $^{15}O$, $^{18}F$, $^{68}Ga$, and $^{82}Rb$. The results are discussed with respect to the ultimate spatial resolution obtained in a scintigraphic image.***

In recent times there has been renewed interest in scintigraphic imaging of positron emitters, particularly in connection with three-dimensional tomography using positron annihilation photon coincidence detection (*1–4*). This has prompted us to obtain more detailed information on positron ranges, penetration depths, and range distributions, which we believe are relevant to the final image resolution and ultimate design factors for positron cameras.

The terms "range" and "path length" (or sum of collision lengths) have been widely used in a somewhat ambiguous manner. According to well-known range–energy relations, the path length $\gamma$ is given by the following (*5*):

$$\gamma(T) = \int_0^{T_0} \left[ -\frac{1}{\rho} \left( \frac{dE}{dx} \right)_{coll} \right]^{-1} dt \qquad (1)$$

where $\frac{1}{\rho}\frac{dE}{dx}$ represents the stopping power of the medium and T is the kinetic energy of the electrons.

The path length has been misused as "range" on several occasions. The range, as defined in this paper, is strictly the penetration depth, which can be identified only by such statistical distribution quantities as FWHM and FW(1/10)M (i.e., 90% absorption thickness). The path length is interpreted as the integral of the reciprocal of the stopping power, i.e., the continuous slowing down approximation range. Since electrons and positrons follow a tortuous path in matter, due to elastic and inelastic scattering by atoms, the range derived from the continuous slowing down approximation appears much larger than the range defined in this paper. Also, since the "range" of the positron is so much smaller than the "path length" (*6–8*), and possibly smaller than the resolution of the camera itself (*9*), neither estimates from the range–energy table using the continuous slowing down approximation nor direct measurements using existing positron-imaging devices can correctly reveal the actual "range" or penetration depth, the factor that ultimately causes the image blurring.

In the present paper, the quantitative results of direct experimental determination of positron ranges are given for a number of clinically used positron-emitting radionuclides. Observation of the images obtained with existing imaging devices can only qualitatively describe the phenomenon (*10*). The purpose of the present paper is, therefore, to determine the "intrinsic" uncertainty in an image obtained with a positron-imaging device so that its clinical effect can be predicted.

## EXPERIMENTAL ARRANGEMENT AND RESULTS

Figure 1 shows the experimental arrangement used for the determination of the absolute positron range distributions for six clinically useful radionuclides. The source, an aqueous solution of the radionuclide in a polystyrene tube (1.39 mm inner diameter), was moved in the y direction in a 38-mm-wide water tank placed between two carefully aligned well-shielded lead collimators of 3.17 mm diameter and 50.8 mm length.

Fast anode pulses from two NaI(Tl) + PM tube detectors were fed to the time-to-pulse-height converter through the time pick-off units (timing filter amplifier + constant fraction discriminator). The pulses within the time resolution of ±10 nsec were then selected by a single-channel analyzer and fed

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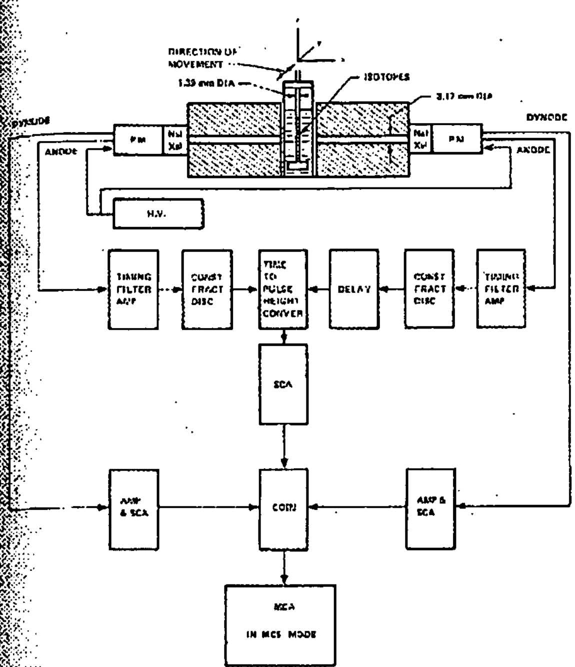


**FIG. 1.** Setup for positron range experiment.

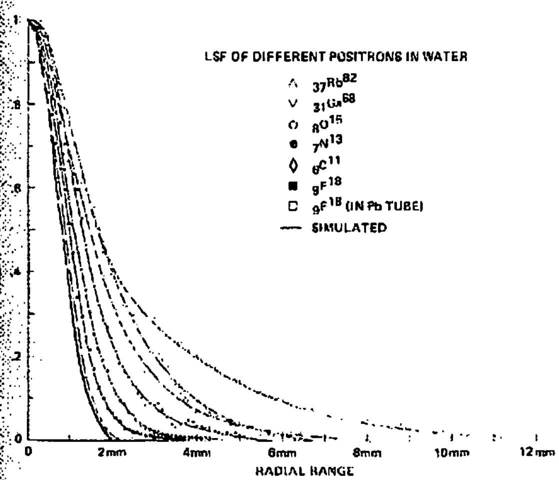


**FIG. 2.** Line spread functions of different positrons in water.

to the slow triple-coincidence unit. Coincident events fulfilling the present energy condition (the selected energy interval was 300–560 keV) were then fed to a multichannel analyzer operated in a multichannel scaling mode and synchronized with a motor that moved the source tube.

In Fig. 2, the experimentally observed range distributions are shown. The curve with open squares is the near-ideal case, namely zero positron range, obtained with a $^{18}F$ source sealed in a lead tube with 1.39 mm inner diameter and 1 mm thickness. This ideal experimental case (zero positron range) agrees very well with the computer-simulated results; the heavy line shown in the figure is the simulated result taking into account the line character of the tube. It also agrees with the 50% isosensitivity response at the center, which is 0.4 of the collimator radius. As expected, the broadening of the range distribution increases with the increase of the maximum and most probable energies of the emitted positrons.

Since the collimators' contribution to the range distribution is small for the high-energy positrons emitted from $^{15}O$, $^{68}Ga$, or $^{82}Sr$*, the indicated FW(1/10)M is mainly due to the range of the positrons. One-half of the FW(1/10)M corresponds to the thickness of the material within which 90% of the particles are stopped, and it can be defined as the "effective range" R of the positrons. The ratio of R to the path length calculated by the continuous slowing down approximation (Eq. 1) is as low as one-third for $^{82}Sr$ and as high as one-half for $^{11}C$.

It is uncertain why there is a substantial difference in FWHM between $^{15}O$ and $^{68}Ga$ and almost no difference between $^{68}Ga$ and $^{82}Rb$ (which has a much higher maximum as well as a higher most probable energy). The FW(1/10)M, however, is considerably different in either case.

Table 1 summarizes the maximum energies, most probable energies, half-lives, theoretically calculated path lengths, and FWHM and FW(1/10)M radial

* The notation $^{82}Rb$ or $^{82}Sr$ is used in this paper to represent an equilibrium mixture of $^{82}Rb$ and $^{82}Sr$.

**TABLE 1. POSITRON-EMITTING ISOTOPES**

| | $^{18}F$ | $^{11}C$ | $^{13}N$ | $^{15}O$ | $^{68}Ga$ | $^{82}Sr$ ($^{82}Rb$) |
|---|---|---|---|---|---|---|
| Maximum energy (MeV) | 0.633 | 0.959 | 1.197 | 1.738 | 1.898 | 3.148 |
| Most probable energy (MeV) | 0.2025 | 0.326 | 0.432 | 0.696 | 0.783 | 1.385 |
| Half-life (min) | 109.7 | 20.3 | 10.0 | 2 | 68.3 | 1.3 |
| Path length for electron of same maximum energy in water (cm) | 0.239 | 0.498 | 0.535 | 0.822 | 0.908 | 1.561 |
| Radial range in water (exp)* FWHM (cm) | 0.102 | 0.111 | 0.142 | 0.149 | 0.168 | 0.169 |
| Radial range in water (exp)* FW(1/10)M (cm) | 0.18 | 0.219 | 0.278 | 0.357 | 0.395 | 0.58 |

* For line source of 0.1397 cm diameter with 0.3175-cm-diameter collimator.

ranges for the six most commonly used positron-emitting radionuclides.

## CONCLUSION

The line spread functions produced by positron-emitting radionuclides are smaller than would be predicted solely on the basis of the conventional "range path length" concept. The main reasons are the tortuous path of a positron during collisions with atomic electrons, and the fact that the most probable energy is substantially lower than the indicated maximum energy.

Since actual line spread functions observed with most of the radionuclides were smaller than 3 mm FWHM, there will probably not be a significant loss in spatial resolution in actual scanners or cameras. It appears, however, that with high-energy positron emitters (e.g., $^{82}$Sr) the line spread contribution due to a relatively large FW(1/10)M (11.6 mm) might affect images obtained with high-resolution positron cameras (*10–12*).

## ACKNOWLEDGMENT

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## Basic principles of magnetic resonance contrast agents.

**Kirsch JE.**

Diagnostic Radiology and Biomedical Engineering, University of Kentucky, Lexington.

The use of contrast agents in MRI is well established as a means to improve diagnosis. MRI differs from other imaging modalities because signal and contrast are multiparametric in both the properties of the tissue and the method of measurement. Contrast depends on differences in proton-spin density, magnetic susceptibility, molecular diffusion and perfusion, and T1 and T2 relaxation times. Relaxivity contrast agents, those that focus on shortening relaxation times, are most commonly employed in the form of paramagnetic chelates and depend on a variety of mechanisms, including concentration, number of ion-coordination sites, spin quantum number, magnetic moment, ion-to-proton distance, and correlation time constants characteristic of the chemical and molecular structure. A sound understanding of the principles of general contrast mechanisms, contrast agent design, and MRI techniques used in conjunction with contrast agents is vital to ensure proper enhancement and optimal diagnostic results.

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1: Magn Reson Q. 1990 Apr;6(2):65-84.

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## Magnetic resonance contrast media: principles and progress.

**Lauffer RB.**

Department of Radiology, Harvard Medical School, Boston, Massachusetts.

The principles and current state of the art for magnetic resonance (MR) imaging contrast media are reviewed. All forms of paramagnetic and superparamagnetic MR contrast agents are covered, including discussions of their effect on MR relaxation and image intensity as well as their chemical and physiological properties.

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1: Radiol Clin North Am. 1988 Sep;26(5):1047-58. Related Articles, Links

## MR contrast agents: an overview.

**Gibby WA.**

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In this article an overview of current and potential MR contrast agents is given. The mechanism of action of contrast agents and their relationship to both T1 and T2 relaxation are explored. Both paramagnetic and superparamagnetic substances are considered. Various physical states of these materials, including small ionic, lipophilic, and macromolecular forms are explored as possible contrast agents. Several clinical examples are given and speculation is made about the future potential of MR contrast agents.

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1: Semin Nucl Med. 1983 Oct;13(4):364-76. Related Articles, Links

## Paramagnetic contrast agents in nuclear magnetic resonance medical imaging.

**Mendonca-Dias MH, Gaggelli E, Lauterbur PC.**

Relaxation time differences are the sources of most of the contrast observed in proton NMR images, not only among normal organs and tissues but between lesions and the adjacent tissue. Although these differences are often large, there are low-contrast situations in which it would be desirable to increase the visibility of an organ or region. The study of time-dependent phenomena would also be aided by the ability to change selected relaxation times deliberately. One way to achieve these goals is to administer substances that change proton relaxation times in tissues without causing significant toxic effects or other physiologic changes. Paramagnetic ions and molecules, those with unpaired electrons, may be useful for this purpose because the very large magnetic effects associated with such electrons can drastically decrease water proton relaxation times at concentrations of the order of 100 to 1000 microM, which may be reached in certain organs after doses of 10 to 100 microM/kg. The general characteristics of such paramagnetic substances are described, and specific animal experiments with manganous ion and its complexes, and with stable nitroxide free radicals and molecular oxygen, are reviewed. The paramagnetic contrast agents already studied are effective, and many more are potentially possible, but the most important questions to be answered are whether acute and chronic toxicity are low enough to permit research and diagnosis on humans.

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1: Top Magn Reson Imaging. 2001 Aug;12(4):309-14. Related Articles, Links

# Safety of magnetic resonance contrast media.

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Intravenous contrast media, specifically the gadolinium chelates, are well accepted for use in the clinical practice of magnetic resonance imaging. The gadolinium chelates are considered to be very safe and lack (in intravenous use) the nephrotoxicity found with iodinated contrast media. Minor adverse reactions, including nausea and hives, occur in a low percentage of cases. The four agents currently available in the United States cannot be differentiated on the basis of these adverse reactions. Severe anaphylactoid reactions are also known to occur with all agents, although these are uncommon. This review discusses the safety issues involved with intravenous administration of the gadolinium chelates and off-label use. The latter is common in clinical practice and permits broader application of these agents.

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